Hemodynamic effects of prostaglandin E_1 infusion in patients with acute myocardial infarction and left ventricular failure

Prostaglandin E_1 (PGE_1) has been shown to limit infarct size, improve coronary blood flow, inhibit platelet aggregation, and reduce both left ventricular (LV) preload and afterload in experimental animals. Its use in the therapy of patients with acute myocardial infarction (AMI) and congestive heart failure (CHF) has not, however, been reported. Five patients with AMI of less than 12 hours' duration and LV dysfunction were studied to assess the hemodynamic effects of IV infusion of PGE_1. PGE_1 in the concentration of 0.4 μg/ml was infused at a rate of 0.003 μg/kg/min (3 ng · kg^{-1} · min^{-1}) to a maximum rate of 0.021 μg/kg/min (21 ng · kg^{-1} · min^{-1}) for a total time of up to 90 minutes. There was an insignificant increase in heart rate, with significant decreases in mean arterial blood pressure and systemic vascular resistance. Pulmonary capillary wedge pressure declined from 21 ± 3 to 15 ± 1 mm Hg ($p < 0.05$), mean pulmonary artery pressure and pulmonary vascular resistance decreased ($p < 0.05$), with increases in cardiac index from 2.38 ± 0.08 to 2.89 ± 0.58 L/min/m^2 ($p < 0.01$) and stroke volume from 51 ± 17 to 59 ± 20 ml/beat ($p < 0.05$). No major cardiac or extracardiac side effects were encountered during PGE_1 infusion. One patient had transient nausea which did not require discontinuation of the drug. PGE_1 is an effective vasodilator and deserves further application in therapy for AMI patients with CHF. (Am Heart J 103:485, 1982.)

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Prostaglandin E_1 (PGE_1) has been shown to improve coronary blood flow,[1-4] reduce both left ventricular (LV) preload and afterload,[2-5] decrease platelet aggregation,[6] and limit infarct size in animals.[7,8] Recent animal studies have shown that PGE_1 significantly reduces cardiac work and diminishes ST segement elevation during myocardial ischemia.[9] Its use in therapy for patients with acute myocardial infarction (AMI) and LV dysfunction has not, however, been reported. In part, the lack of PGE_1 application in clinical AMI appears to be the result of concern about gastrointestinal or other distressing side effects. The purpose of the present patient study was to determine whether administration of PGE_1 could beneficially alter the hemodynamic disturbances associated with AMI without adverse side effects.

METHODS

Patient population. Five patients, including three men and two women ages 46 to 72 years (mean age, 64 years), with AMI of less than 12 hours' duration and LV dysfunction, were studied. LV dysfunction was defined by the presence of bibasilar pulmonary rales and/or third heart sound and LV filling pressure (LVFP) of more than 15 mm Hg. Four patients had ECG evidence of anterior and one of inferior transmural AMI. The diagnosis of transmural infarction was based on ECG findings of acute ST segment elevation followed by development of pathologic Q waves or substantial decrease in R wave voltage, coincident with serum myocardial enzyme changes typical of AMI. Three patients were in Killip class II and two patients were in Killip class III.[10] Conventional treatment, including sedation, oxygen, narcotics, and antiarrhythmic agents such as lidocaine, was prescribed when indicated but the administration of any vasodilators, diuretics, or other agents with known substantive hemodynamic effects was withheld until hemodynamic study of PGE_1 had been completed.

Hemodynamic determinations. The patients were admitted to the coronary care unit and informed consent was obtained. A 7F Lexington thermodilution catheter was positioned in the pulmonary artery (PA) via an antecubital vein cutdown and a short plastic catheter was inserted percutaneously into the radial artery. PA pressure and systemic arterial pressure (AP) were monitored simultaneously by use of Statham P231D and Bently 800 transducers, respectively. Cardiac output (CO) was measured by the thermodilution technique with the use of 10 ml of sterile normal saline at room temperature. Each CO recorded was the mean of at least two consecutive deter-

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Received for publication July 6, 1981; accepted July 24, 1981.

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0002-8703/82/040485 + 05$00.50/0

Table I. Peak hemodynamic responses during PGE_1 infusion in AMI

	HR (bpm)	*MAP (mm Hg)*	*PCW (mm Hg)*	*MPAP (mm Hg)*	*CI (L/min/m²)*	*SV (ml)*	*SVR (dyne · sec · cm⁵)*	*PVR (dyne · sec · cm⁵)*	*PAR (dyne · sec · cm⁵)*
Control	78 ± 18	101 ± 8	21 ± 3	27 ± 4	2.38 ± 0.08	51 ± 17	1710 ± 527	509 ± 124	123 ± 52
PGE_1	83 ± 18	92 ± 5	15 ± 1	21 ± 3	2.89 ± 0.58	59 ± 20	1373 ± 423	323 ± 80	89 ± 44
p Value	NS	< 0.05	< 0.05	< 0.05	< 0.01	< 0.05	< 0.05	< 0.01	< 0.01

Values expressed as mean ± SEM. PCW = pulmonary capillary wedge pressure; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; NS = not significant ($p > 0.05$).

minations having the maximal variation of less than 10%. The ECG lead with the greatest ST segment elevation was monitored. Blood was drawn for routine hematologic and blood chemistry studies before and during the PGE_1 infusion. Control hemodynamic indices including heart rate (HR), phasic and mean systemic AP, LVFP measured as pulmonary capillary wedge pressure, phasic and mean PA pressure, and CO were determined at least twice at 15-minute intervals before the infusion.

PGE_1 infusion. A solution of PGE_1 (Prestin VR, Upjohn Co., Kalamazoo, Mich.) containing 0.4 μg/ml was prepared with 5% dextrose. PGE_1 infusion, regulated by a Harvard pump (Model 901), was begun in the central venous circulation and the dose was slowly increased every 10 to 15 minutes. Intravenous infusion was increased to 1 to 70 ml/min at 10 minutes and to 3.50 ml/min at 20 to 30 minutes. The desirable hemodynamic effects were achieved at dosage range of 10 to 19 ng · kg^{-1} · min^{-1}, with the average effective dose of 14.6 ng · kg^{-1} · min^{-1}. The infusion rate was modified if systolic AP fell by 20 mm Hg or more, if HR increased more than 20 bpm, or if LVFP fell below 15 mm Hg. Hemodynamic measurements were recorded every 15 minutes for the total infusion time of 90 minutes and for a further 60 minutes after the infusion had been discontinued.

Hemodynamic-related indices calculated. The following indices were derived: SWI = SVI × (MSP − LVFP) × 1.36/100, where SWI represents stroke work index (gm · m/m^2), SVI is stroke volume index (ml/m^2), and MSP is mean systemic pressure (mm Hg). SVR = K (mean aortic pressure)/systemic flow = 80 ($\overline{AO}$)/CO, and PVR = K (mean pulmonary pressure)/pulmonary flow = 80 ($\overline{PA}$)/CO, where SVR represents systemic vascular resistance, PVR is total pulmonary vascular resistance, $\overline{AO}$ is mean aortic pressure, and $\overline{PA}$ is mean pulmonary pressure; K represents the conversion factor from hybrid units of mm Hg · L^{-1} · min^{-1} to metric units of dyne · sec · cm^{-5}. PAR = ($\overline{PA}$ − LVFP × 80)/CO, where PAR is pulmonary arteriolar resistance.

Statistical analysis. Statistical analysis was performed by use of Student's paired *t* test. Numerical values are reported as mean ± SEM.

RESULTS

Hemodynamic effects. The results of control and peak hemodynamic responses during the PGE_1 infusion are shown in Table I. During PGE_1 infusion, HR increased slightly but did not reach statistical significance. However, there were significant decreases in mean systemic arterial pressure (MAP) and mean pulmonary pressure (MPP) (Fig. 1). In addition, LVFP, SVR, PVR, and PAR were significantly reduced by PGE_1 (Figs. 2 and 3), while stroke volume (SV), cardiac index (CI), and SWI were increased (Figs. 2 and 4). Following discontinuation of PGE_1 infusion, all hemodynamic parameters in four of the five patients returned to control values within 30 to 60 minutes. At this point, patients were treated with conventional vasodilators. In one patient, the pulmonary capillary wedge pressure remained normal for up to 2 hours.

Anti-ischemic effects. Three patients had complete relief of their chest pain during PGE_1 infusion. There were, however, no significant ST changes in the monitored precordial lead.

Side effects. No major side effects were encountered during the PGE_1 infusion; in particular there was no abdominal discomfort, vomiting, or diarrhea. However, it should be pointed out that this was a pilot study with only a short duration of infusion. One patient had transient nausea but did not feel this sufficient to discontinue study.

DISCUSSION

Beneficial hemodynamic effects of PGE_1 in AMI with congestive heart failure (CHF) due to balanced systemic arteriovenous dilation. The present study demonstrates that administration of PGE_1 to patients with AMI complicated by CHF results in significant hemodynamic improvement and relief of LV dysfunction without significant tachycardia or other side effects. The lack of substantive untoward extracardiac events such as nausea, vomiting, and diarrhea despite hemodynamic improvement may be related to the relatively small doses of PGE_1 necessary to reduce LVFP and SVR; thereby relieving pulmonary congestion and improving pump output. Although previous animal studies have not suggested an effect of PGE_1 on venous capacitance, the results of the present study demonstrate reduction

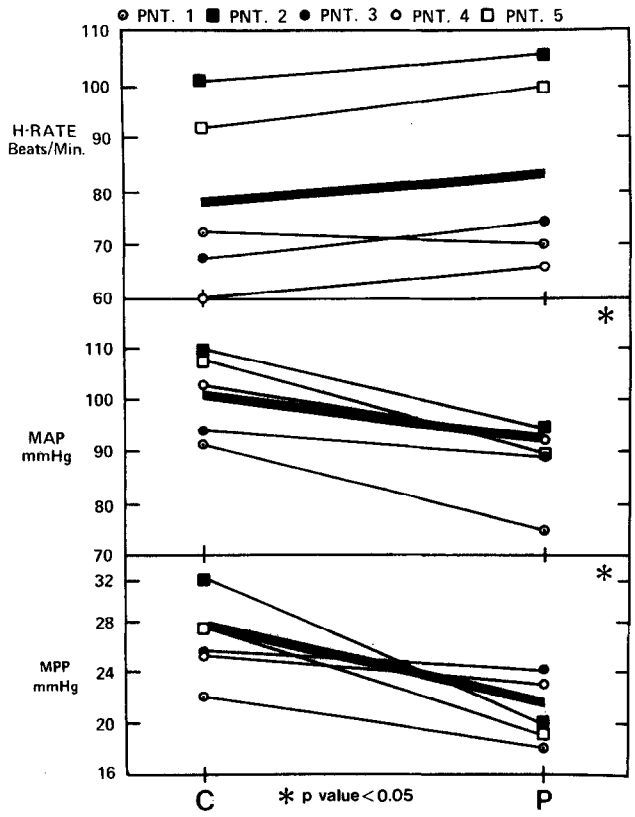

Fig. 1. Control (C) and peak (P) values of heart rate (H-Rate), MAP, and MPP in response to PGE_1 infusion. *PNT* = patient.

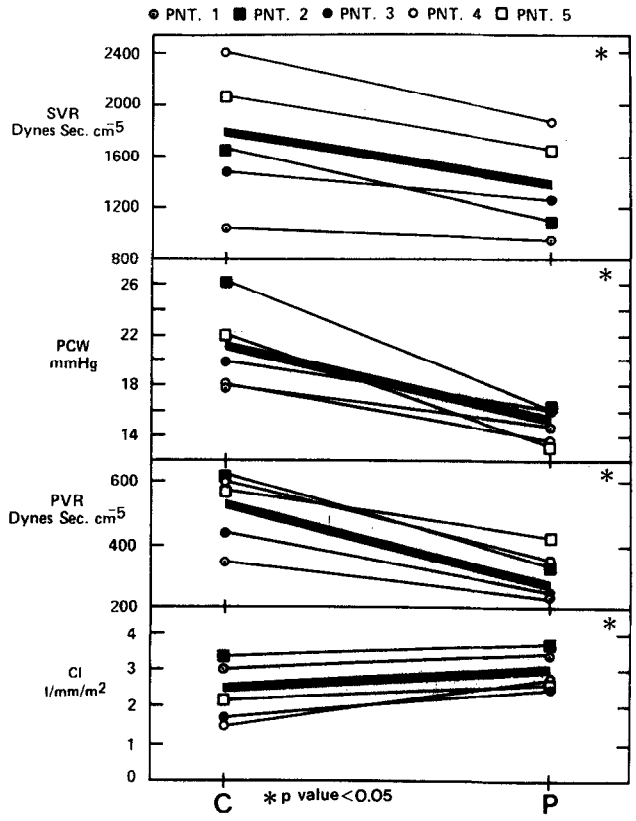

Fig. 2. Control *(C)* and peak *(P)* values of SVR, pulmonary capillary wedge pressure *(PCW)*, PVR, and CI in response to PGE_1 infusion.

of LVFP to normal with moderate decrease in SVR accompanied by only modest rises in SV and CI. Thus, the considerable reduction in LVFP suggests that in AMI patients with CHF, PGE_1 therapy results in systemic venorelaxation.

Potential anti-ischemic properties of PGE_1. Although the present study was designed to examine the acute hemodynamic actions of PGE_1, this agent is also known to have other effects that may be of benefit in myocardial ischemia. PGE_1 has been shown to preserve myocardial cells during ischemia and diminish autolytic processes as evidenced by decreased myocardial creatine kinase (CK) and cathepsin D release and by preservation of myocardial CK activity, indicating protection of cardiac cell integrity.[7,11] PGE_1 increases coronary blood flow and decreases coronary vascular resistance.[1,12] PGE_1 also protects against isoproterenol-induced myocardial injury as evidenced by significant reductions in ST segment elevation and plasma free fatty acid concentration.[13] In addition, PGE_1, inhibits norepinephrine release[14] and the attendant increase in lipolysis, thereby limiting the deleterious myocardial oxygen wasting effect resulting from catecholamine rise during AMI. The coronary vasodilatory action of PGE_1 in conjunction with reduced LV preload might favorably redistribute myocardial perfusion toward the subendocardium, the area most critically compromised during acute ischemia. It is also possible that PGE_1 might increase collateral blood flow directly or by reducing LVFP. Of particular interest is PGE_1 inhibition of platelet aggregation,[15] since recent studies have indicated increased platelet aggregation in AMI patients and a pathogenetic role of such platelet dysfunction in the infarction process.[16-18]

Potential advantages of PGE_1 compared to other vasodilators in AMI. The beneficial hemodynamic effects observed in the present study have also been observed with other vasodilators such as nitroprusside and nitroglycerin.[19,20] However, the use of nitroprusside in the presence of acute myocardial ischemia has been of concern to some workers, since animal studies have suggested that nitroprusside may adversely alter the distribution of myocardial blood flow during experimental infarction.[21,22] Hence, an alternative means of acute afterload reduction appears useful. While not directly compared, the effects of PGE_1 in this study seem similar to the balanced systemic arterial and venous dilation caused by nitroprusside, as shown by the 16%

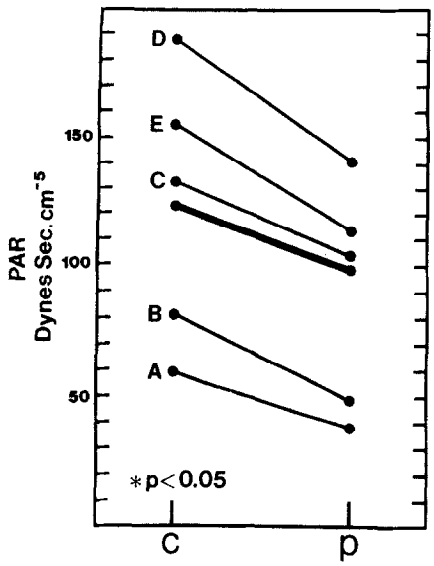

Fig. 3. Control *(C)* and peak *(P)* response values of PAR to PGE_1 infusion.

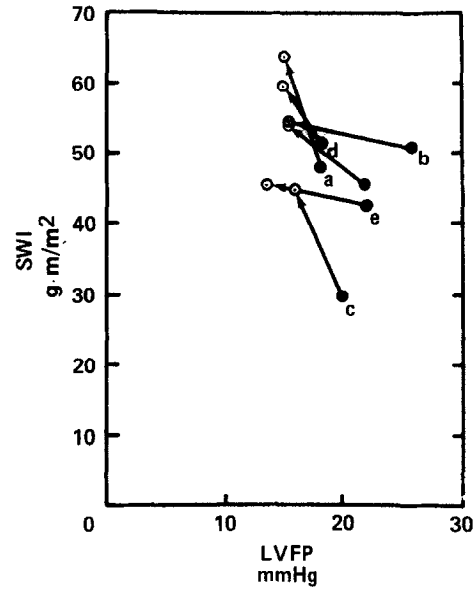

Fig. 4. Effects of PGE_1 infusion on left ventricular function measured as the relation between changes in SWI and LVFP.

increase in SV and 29% reduction in LVFP produced by PGE_1. Nitroglycerin exerts a beneficial hemodynamic effect in AMI patients without increasing ST segment elevation or adversely affecting distribution of myocardial perfusion.[20] However, nitroglycerin does not possess some of the other potential salutary properties of PGE_1 such as inhibition of catecholamine release and diminished platelet aggregation. While another prostaglandin, prostacyclin (PGI_2), provides greater in vitro antiplatelet aggregation and more potent coronary vasodilation compared to PGE_1, the use of PGI_2 in AMI patients with congestive heart failure appears limited due to marked PGI_2-induced systemic vasodilation and hypotension.

Conclusions. Although the number of patients included in the present study was relatively small, the salutary hemodynamic results are significant. In view of our clinical observations and the experimental data of others suggesting additional beneficial actions of PGE_1, this therapeutic agent deserves further evaluation in the management of patients with AMI and LV failure.

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Comparative hemodynamic effects of digoxin vs nitroprusside in conscious dogs with aortocaval fistula-induced chronic left ventricular volume overload and normal systolic performance

We compared the effects of IV digoxin (0.04 mg/kg) and nitroprusside (NP) (1.2 and 1.8 μg/kg/min) on left ventricular (LV) performance in six preinstrumented conscious dogs with chronic volume overload and congestive heart failure (CHF) produced by an aortocaval fistula. At 3 and 6 hours after digoxin administration (serum level, 3.5 ± 0.6 ng/ml), there were no changes in heart rate, LV systolic (LVSP) and end-diastolic (LVEDP) pressures, LV dimensions, LV dP/dt_{max}, or percent minor diameter shortening as compared to control values in the resting state, after beta blockade, or during phenylephrine infusion. By contrast, NP produced a significant reduction ($p < 0.05$) in LVEDP (16 ± 3 to 10 ± 3 mm Hg) at the smaller dose which caused no change in mean aortic pressure. The larger dose of NP further reduced LVEDP and evoked significant ($p < 0.05$) decreases in LVSP (124 ± 5 to 117 ± 7 mm Hg), mean aortic pressure (85 ± 3 to 78 ± 5 mm Hg), and LV end-diastolic dimension (LVEDD) (53.0 ± 5.5 to 52.0 ± 5.7 mm), while augmenting LV dP/dt_{max} (3288 ± 266 to 3647 ± 130 mm Hg/sec). Beta blockade with IV propranolol (2.0 mg/kg) prevented the rise in LV dP/dt_{max} after high-dose NP administration but did not alter the reductions in mean aortic pressure, LVEDP, and LVEDD. This study indicates that NP, but not digitalis, has a favorable effect on LV hemodynamics in the volume-overloaded heart with normal LV systolic contraction and high-output CHF resulting from increased blood volume and reduced LV diastolic compliance. At least part of the apparent improvement in LV performance observed with high-dose NP is sympathetically mediated since it can be attenuated by beta blockade. (Am Heart J 103:489, 1982.)

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The digitalis glycosides have been used to treat patients with congestive heart failure (CHF) for almost 200 years.[1] However, there is still considerable controversy concerning the short- and long-term salutary effects of digitalis on left ventricular (LV) performance in the normal and the failing heart. While most experimental animal and patient studies have demonstrated an enhancement of LV performance by digitalis,[2-17] other studies have demonstrated minor or variable improvement.[18-22] The effects of the cardiac glycosides on LV performance may vary depending on the pretreatment inotropic state, the peripheral vascular resistance, the route of administration, the level of circulating

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Received for publication July 24, 1981; accepted Aug. 10, 1981.

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0002-8703/82/040489 + 09$00.90/0